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The research results, supported by Air Force Grant #F49620-93-1-0337 (1), have been successful in obtaining the above objectives. Research supported by this grant has lead to significant advancement in the area of optical coherence tomography (OCT). In brief, OCT represents a new and valuable diagnostic technique for high-resolution, noncontact imaging of the human eye including the retina and cross-sectional imaging of structures in the anterior segment. Optical coherence tomography is analogous to ultrasound, except that optical rather than acoustic reflectivity is measured. This new optical imaging modality has spatial resolution superior to that of conventional clinical ultrasonography ($<20un$) and high sensitivity (dynamic range, $>90db$). OCT is proving to be a powerful tool for detecting and monitoring a variety of diseases of the eye including a variety of macular diseases, such as macular edema, macular holes, and detachments of the neurosensory retina and pigment epithelium.

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Final Technical Report: Air Force Grant # F49620-93-I-0337(1)

Dates of Contract: 11/15/92-04/30/95

Principal Investigator: Carmen A. Puliafito, MD
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Goal of Study:

The objective of Air Force Grant # F49620-93-I-0337(1) was to develop methods for
the study retinal injury. Specifically, mechanisms resulting from picosecond laser
exposures, and to measure retinal injury thresholds from single and multiple picosecond
laser pulses. Both in vitro and in vivo experiments were to be performed. Retinal injury
mechanisms were to be investigated for laser intensities both below and above optical
breakdown threshold. Damage was to assessed at a the retinal pigment eptithelium (RPE)
level.

Objectives also included methods to demonstate a new technique for noninvasive,
noncontact, micron resolution cross sectional imaging of the retina in vivo. Methods
used to achieve these objectives centered on the advancement of optical coherence

tomography (OCT) and to determine the potential applications and protocols of OCT for ocular diagnostics. In the process, the potential of OCT for applications in noncontact biometry, anterior chamber angle assessment, identification and monitoring of intraocular masses and tumors, and elucidation of abnormalities of the cornea, iris, and crystalline lens was also assessed.

Results:

To date, the research results, supported by Air Force Grant # F49620-93-I-0337(1), have been successful in obtaining the above objectives. Research supported by this grant has lead to significant advancement in the area of optical coherence tomography (OCT). In brief, OCT represents a new and valuable diagnostic technique for high-resolution, noncontact imaging of the human eye including the retina and cross-sectional imaging of structures in the anterior segment. Optical coherence tomography is analogous to ultrasound, except that optical rather than acoustic reflectivity is measured. This new optical imaging modality has spatial resolution superior to that of conventional clinical ultrasonography ($<20\mu m$) and high sensitivity (dynamic range, >90db). OCT is proving to be a powerful tool for detecting and monitoring a variety of diseases of the eye including a variety of macular diseases, such as macular edema, macular holes, and detachments of the neurosensory retina and pigment epithelium.

Specifically, research in part funded by Air Force Grant # F49620-93-I-0337(1) has led to the following.

1) Pioneering work in the development and refinement of high-speed optical coherence domain reflectometry.

2) The extension of the technique of low coherence reflectometry to tomographic imaging in biological systems.

3) Noncontact, high resolution measurements of anterior eye structures.

4) The first in vivo measurements of human retinal structure with optical coherence tomography.

5) Optical coherence tomographs which can discriminate the cross-sectional morphologic features of the fovea and optic disc, the layered structure of the retina, and normal anatomic variations in retinal and retinal nerve fiber layer thickness with 10-μm depth resolution.

6) Direct in vivo measurements with micrometer-scale resolution of corneal thickness and surface profile, anterior chamber depth and angle, and iris thickness and surface profile.

7) Correlation of fundus examination and fluorescein angiography with OCT with mutltiple different pathologies.

#1 HIGH-SPEED IN VIVO RETINAL IMAGING WITH OPTICAL COHERENCE TOMOGRAPHY ((J.A. Izatt, M.R. Hee, D Huang, E.A. Swanson, C.P. Lin, J.S. Schuman, C.A. Puliafito and J.G. Fujimoto)) Dept. of EECS/RLE, MIT, Cambridge, MA 02139; M.I.T. Lincoln Lab., Lexington, MA 02173; New Eng. Eye Cent., Tufts U. School of Med., Boston, MA 02113.

Purpose. To demonstrate a new technique for noninvasive, noncontact, micron resolution cross sectional imaging of the retina in vivo and to report preliminary results on measurement reproducibility. **Methods.** Optical Coherence Tomography (OCT) utilizes low-coherence light and interferometry to obtain tomographic images of optical backscatter in biological tissue with high-sensitivity (>90dB) and micron-scale resolution. A new high-speed OCT instrument has been developed for clinical examination of the eye using a compact diode laser and fiber optic system interfaced to a standard slitlamp biomicroscope. Tomographic images with arbitrary scan patterns at selected locations on the retina are obtained under operator control. Image formation is displayed on computer

in false color in real time. The acquisition time for a typical 100 x 500 pixel retinal image is 2.5 seconds. **Results.** Images of the macular and papillary regions with 14 micron depth resolution have been obtained in normal human subjects. Retinal topography, such as the contours of the foveal pit and the optic nerve head are directly measured. Retinal substructure is measurable with differentiations of the retinal nerve fiber layer (RNFL), inner and outer plexiform layers (IPL, OPL), and choriocapillaries. Preliminary measurements of RNFL and retinal thickness obtained in given subjects at specified retinal locations are reproducible to within the device resolution. A preliminary protocol for the examination of the normal human retina is reported. **Conclusions.** To the best of our knowledge, OCT achieves the highest resolution, noninvasive images of retinal structure that have been obtained to date. Preliminary measurements of the retina suggest that OCT may be a powerful diagnostic for early detection and monitoring of ocular diseases such as macular degeneration, edema, and glaucoma.

#2) IN VIVO OPTICAL COHERENCE TOMOGRAPHY OF THE ANTERIOR SEGMENT ((M.R. Hee, J.A. Izatt, E.A. Swanson, D Huang, C.P. Lin, J.S. Schuman, C.A. Puliafito, J. Inderfurth, R. Birngruber, J.G. Fujimoto)) Dept of EECS/RLE, M.I.T., Cambridge, MA 02139; M.I.T. Lincoln Lab., Lexington, MA 02173; New Eng. Eye Cent., Tufts U. School of Med., Boston, MA 02111; Medical Laser Center, Lubock, Germany.

Purpose. We describe a new technique for noncontact, noninvasive, high-resolution cross-sectional tomography of the anterior eye and discuss potential clinical applications. **Methods.** Optical Coherence Tomography (OCT) is a technique for cross-sectional imaging in tissue based on low-coherence interferometry. OCT functions analogously to ultrasound B-scan, except that it uses optical waves to obtain two-dimensional, cross-sectional images of the eye with ~10μm lateral and longitudinal resolution and sensitivity to weakly backscattered light exceeding 95db. A high-speed, compact fiber optic OCT scanner has been developed which is coupled to a standard slit-lamp ophthalmascope. A typical 100X500 pixel image of the full anterior chamber is obtained in under 7s. In vivo tomography of the anterior segment was conducted in normal human eyes and post-operatively in rabbit eyes after Ho:YSCC laser thermokeratoplasty. **Results.** Tomographs of the human chamber depth and angle, corneal thickness and curvature, refractive power, and iris biometry, narrow-angle glaucoma diagnosis, the identification and monitoring of keratorefractive surgeries. Post-keratoplasty imaging performed in rabbit eyes provides a quantitative microscopic anatomy including peri-operative corneal refractive changes as well as visualization of microscopic anatomy including peri-operative corneal edema, corneal endothelium, and epithelial damage and healing. **Conclusion.** OCT is a versatile, clinically relevant technique for high-resolution, non-contact imaging of the anterior eye.

#3) BLOOD REFLECTIVITY IN OPTICAL COHERENCE TOMOGRAPHY

((D. Huang, M.R. Hee, E.A. Swanson, J.G. Fujimoto, J.S. Schuman, C.A. Puliafito))
Massachusetts Institute of Technology; New England Eye Center, Tufts University
School of Medicine.

Purpose. To determine the contribution of blood in the backscattered signal in optical coherence tomography (OCT). **Methods.** OCT retinal images from a live subject are compared with the OCT signal from blood in vitro. **Results.** OCT is a micron resolution imageing technique than can noninvasively capture cross-sectional retinal images with delineation of internal layers. The instrument is clinically useful for the examination of retinal diseases and glaucoma. In OCT retinal images, the inner choroid appears as a highly backscattering layer, in sharp contrast to the weakly scattering photoreceptor layer. We also measured the OCT reflectivity of blood in vitro. The reflectivity of inner choroid and blood is -87dB/mm. **Conclusion.** Blood is a major contributer to backscattered OCT signals from the choroid and blood-filled structures should appear bright in OCT images. Because of rapid subjacent structures. This may explain the weakening of signal from the outer choroid and sclera in OCT images. Supported by National Institute of Health grant RO1-GM3459-06, U.S. Office of Naval Research Medical Free Electron Laser Program grant N00014-91-C-0084, the Johnson and Johnson Foundation, and the U.S. Department of the Air Force.

Air Force Grant # F49620-93-I-0337 contributed to the following published papers:

#1 MICRON-RESOLUTION RANGING OF CORNEA ANTERIOR CHAMBER BY OPTICAL REFLECTOMETRY

D. Huang, SM, Jyhpyng Wang, PhD, C.P. Lin, PhD, C.A. Puliafito, MD, and James G. Fujimoto, PhD

Department of Electrical Engineering and Computer Science and Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge Massachusetts, 02139 (D.H., J.W., J.G.F.), and Department of Ophthalmology, Harvard Medical School and the Laser Research Laboratory, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts 02114 (C.P.L., C.A.P.)

Noncontact, high resolution measurements of anterior segment eye structures using optical coherence domain reflectometry are described. Distances between intraocular structures are measured by directing a beam of short coherence length light onto the eye and performing and interferometric measurements on the optical group delay reflected signals. Measurements of corneal thickness, corneal excision depth, and anterior chamber depth are demonstrated in vitro, and the location of tissue boundaries is resolved to within +/- 2µm. The full-width-half-maximum longitudinal resolution is 10µm. Sensitivities to reflected signals as small as 10^{-10} of incident power are achieved by heterodyne detection

#2 HIGH-SPEED OPTICAL COHERENCE DOMAIN REFLECTOMETRY

E.A. Swanson, , D. Huang, M.R. Hee, J.G. Fujimoto, Department of Electrical Engineering and Computer Science, MIT, C.P. Lin, and C.A. Puliafito, Laser Research Laboratory, New England Eye Center, Tufts University School of Medicine. Opt. Lett. 17:151-153(1992)

Summary. We describe a high-speed optical coherence domain reflectometer. Scan speeds of 40mm/s are achieved with a dynamic range >90 dB and a spatial resolution of 17µm. Two applications are presented: the noninvasive measurement of anterior eye structure in a rabbit in vivo and the characterization of reflections and interelement spacing in a multielement lens.

#3 IN VIVO RETINAL IMAGING BY OPTICAL COHERENCE TOMOGRAPHY

E.A. Swanson, Lincoln Laboratory, MIT, J.A. Izatt, M.R. Hee, D. Huang, Department of Electrical Engineering and Computer Science, MIT, C.P. Lin, J.S. Schuman, and C.A. Puliafito, Laser Research Laboratory, New England Eye Center, Tufts University School of Medicine, and J.G. Fujimoto, Department of Electrical Engineering and Computer Science, MIT. Opt. Lett. 18:1864-1866 (1993)

Summary. We describe what are to our knowledge the first in vivo measurements of human retinal structure with optical coherence tomography. These images represent the highest depth resolution in vivo retinal images to date. The tomographic system, image-processing techniques, and examples of high-resolution tomographs and their clinical relevance are discussed.

#4 MICROMETER-SCALE RESOLUTION IMAGING OF THE ANTERIOR EYE IN VIVO WITH OPTICAL COHERENCE TOMOGRAPHY

J.A. Izatt, PhD; M.R. Hee, MS; E.A. Swanson, MS; C.P. Lin, PhD; D. Huang, MD, PhD; J.S. Schuman, MD; C.A. Puliafito. MD, J. Fujimoto, PhD.

Objective: To demonstrate a new diagnostic technique, optical coherence tomography, for high resolution cross-sectional imaging of structures in the anterior segment of the human eye in vivo. Optical coherence tomography is a new, noninvasive, noncontact optical imaging modality that has spatial resolution superior to that of conventional ultrasonography (<20μm) and high sensitivity (dynamic range, >90dB).
Design: Survey of intraocular structure and dimension measurements.
Setting: Laboratory
Patients: Convenience sample
Main Outcome Measures: Correlation with range of accepted normal intraocular structure profiles and dimensions
Results: Direct in vivo measurements with micrometer-scale resolution were performed of corneal thickness and surface profile (including visualization of the corneal epithelium), anterior chamber depth and angle, and iris thickness and surface profile. Dense nuclear cataracts were successfully imaged through their full thickness in a cold cataract model in calf eyes in vitro.
Conclusion: Optical coherence tomography has potential as a diagnostic tool for applications in noncontact biometry, anterior chamber angle assessment, identification and monitoring of intraocular masses and tumors and elucidation of abnormalities of the cornea. iris, and crystalline lens.

#5 OPTICAL COHERENCE TOMOGRAPHY OF THE HUMAN RETINA

M.R. Hee, MS; J. Izatt, PhD; E.A. Swenson. MS; D. Huang, MD, PhD; J. S. Schuman, MD. C.P. Lin. PhD; C.A. Puliafito. MD; J.G. Fujimoto, PhD. Optical Coherence Tomography of the Human Retina.

Objective: To demonstrate optical coherence tomography for high-resolution, noninvasive imaging of the human retina. Optical coherence tomography is a new imaging technique analogous to ultrasound B scan that can provide cross-sectional images of the retina with micrometer-scale resolution.
Design: Survey optical coherence tomographic examination of the retina, including the macula and optic nerve head in normal human subjects.
Setting: Research laboratory
Participants: Convenience sample of normal human subjects.
Main Outcome Measures: Correlation of optical coherence retinal tomographs with known normal retinal anatomy.

Results: Optical coherence tomographs can discriminate the cross-sectional morphologic features of the fovea and optic disc, the layered structure of the retina, and normal anatomic variations in retinal and retinal nerve fiber layer thickness with 10μm depth resolution.

Conclusion: Optical coherence tomography is a potentially useful technique for high-depth resolution, cross sectional examination of the fundus.

#6 IMAGING OF MACULAR DISEASES WITH OPTICAL COHERENCE TOMOGRAPHY

C.A. Puliafito, MD, M.R. Hee, MS. C.P. Lin, PhD, E. Reichel, J.S. Schuman, MD, J.S. Duker, MD, J.A. Izatt, PhD, E.A. Swanson, MS, J.G. Fujimoto, PhD.

Background/Purpose: To assess the potential of a new diagnostic technique called optical coherence tomography for imaging macular disease. Optical coherence tomography is a novel noninvasive, noncontact imaging modality which produces high depth resolution (10μm) cross-sectional tomographs of ocular tissue. It is analogous to ultrasound, except that optical rather than acoustice reflectivity is measured.

Methods: Optical coherence tomography images of the macula were obtained in 51 eyes of 44 patients with selected macular diseases. Imaging is performed in a manner compatible with slit-lamp indirect bimicroscopy so that high-resolution optical tomography may be accomplished simultaneously with normal ophthalmic examination. The time-of-flight delay of light backscattered from different layers in the retina is determined using low-coherence interferometry. Cross-sectional tomographs of the retina is determined using low-coherence interferometry. Cross-sectional tomographs of the retina profiling optical reflectivity versus distance into the tissue are obtained in 2.5 seconds and with a longitudinal resolution 10μm.

Results: Correlation of fundus examination and fluorescein angiography with optical coherence tomography tomographs was demonstrated in 12 eyes with the following pathologies: full- and partial-thickness macular hole, epiretinal membrane, macular edema, intraretinal exudate, idiopathic central serous chorioretinopathy, and detachments of the pigment epithelium and neurosensory retina.

Conclusion: Optical coherence tomography is potentially a powerful tool for detecting and monitoring a variety of macular diseases, including macular edema, macular holes, and detachments of the neuro-sensory retina and pigment epithelium.